Comments of Dr. Graham W. Gibbs, prepared for the American Chemistry Council Crystalline Silica Panel

These Comments focus on key issues raised by the April 2003 Review Draft *Chronic Toxicity Summary, Silica (Crystalline, Respirable)* ("Chronic Toxicity Summary" or "CTS"), which was prepared by the California Office of Environmental Health Hazard Evaluation ("OEHHA") in order to derive a Reference Exposure Level ("REL") for Crystalline Silica. The Comments were prepared by Dr. Graham W. Gibbs, President of Safety Health Environment International Consultants Corp. and Adjunct Full Professor, University of Alberta, at the request of the American Chemistry Council's Crystalline Silica Panel. Dr Gibbs' Curriculum Vitae and a list of his publications are attached.

Many of the issues addressed in these Comments are discussed at greater length in a report by Gibbs, Berry and Muir (1999) entitled "Assessing the Risk of Non-Malignant Respiratory Diseases in Workers Exposed to Silica." A copy of that report is attached as Appendix A. Also attached (as Appendix B) is a copy of the recent paper by Gibbs and Du Toit (2002), *Estimating the Quartz Exposure of South African Gold Miners*. Ann. Occup. Hyg. 46: 597-607. That paper has an important impact on risk estimates derived from the South African gold miner study.

In my view, there are three important issues.

Comment 1. First, the study of the South African Gold Miners by Hnizdo and Sluis-Cremer (1993) is the key study for the risk estimates derived in section VI of the Chronic Toxicity Summary. Recent work by Gibbs and Du Toit (2002) shows that the exposure estimates in the South African studies are most probably underestimated by a factor of about 2. This has the effect of dramatically reducing the estimated risk of silicosis per unit exposure, as the exposure-response relationship is curvilinear. (See the bottom of page 602 in Gibbs & Du Toit 2002). The data as described in the CTS have not been adjusted to take this underestimation of exposure into account.

      Response. OEHHA s*taff reviewed the Gibbs and Du Toit (2002) paper. Based on the data in that paper, the exposure to silica is believed by Gibbs and Du Toit to be underestimated by a factor of 1.8 (54%/30%). However, OEHHA staff analysed the data from Page-Shipp and Harris (1972) on which both Hnizdo and Sluis-Cremer (1993) and Gibbs and Du Toit (2002) relied, and confirmed that the value of 30% was properly applied. It appears that some confusion was caused by an incorrect footnote to a table in Hnizdo and Sluis-Cremer(1972), but that their analysis of silica exposures for particular occupations is correct. This is discussed in the revised chronic REL summary, in OEHHA's response to Comment 3 by the American Chemistry Council, and in OEHHA's Response to Comment 8 below. In addition, there are other estimates of percent quartz in the dust from the South African gold mines, which indicate that even lower values may also be plausible.*

Comment 2. Second, one of the studies quoted as supporting the REL, Steenland & Brown (1995), is one which the authors of the CTS justifiably criticize as the basis for deriving an exposure-response relationship. The other "supportive" study, Hughes et al (1998), involved workers in the diatomaceous earth (DE) industry exposed to cristobalite. While it is a well conducted study, there still remain issues concerning the cristobalite exposure levels - which apparently were based on the product content of cristobalite, not airborne respirable cristobalite concentrations - and the identification of the exposure category that can properly be considered a LOAEL.

Response. *Staff is aware that there are no perfect studies available. Uncertainty in exposure estimates is a very common problem and does not automatically preclude derivation of a Reference Exposure Level. It is part of the uncertainty in risk assessment and in fact goes both ways (underestimation and overestimation). OEHHA derived an estimate of the chronic REL from Steenland and Brown and other papers for comparative purposes. The data in most studies suggest a range for the chronic REL of 3 to 10 $\mu g/m^3$. As noted, OEHHA did not choose this study as the basis of the proposed chronic REL for crystalline silica.*

Comment 3. Third, the proposed REL of 3 micrograms per cubic metre is at least one order of magnitude lower than the median/average exposure of workers in the various industries studied. According to Mannetje et al. (2002), the median/average concentration of crystalline silica to which Diatomaceous Earth workers were exposed was 180 $\mu g/m^3$; for Finnish Granite workers, it was 590 $\mu g/m^3$; and for US gold miners, it was 50 $\mu g/m^3$. The average crystalline silica concentration for the South African Gold miners for the period 1947-1970 (before any exposure adjustment) was reported as 90 $\mu g/m^3$ (Hughes & Weill 1995). Thus, the derivation of an environmental REL on the basis of occupational studies involves significant extrapolation and reflects the assumption that cumulative exposure is the relevant metric, regardless of how the exposure is accumulated. In particular, it assumes that relatively high levels of exposure for shorter periods of time in the occupational setting present the same risks as much lower levels of exposure for a longer period term (i.e., continuous lifetime exposure) in the environmental setting. There are two problems with this assumption.

(1) It ignores the possibility of a dose-rate effect, which a number of studies suggest exists. For example, as noted in Table 13 of the CTS, Hughes et al (1998) found that for cristobalite, there were two different exposure-response curves - one for workers exposed at high average concentrations (above 500 $\mu g/m^3$) and the other for workers exposed at lower concentrations (below 500 $\mu g/m^3$). Similarly, in a study of Scottish colliery workers, Buchanan et al. (2001) found that indices based on the square of concentration (as opposed to simple cumulative exposure) gave the best fits. This index estimates higher risks at high exposures than an index based on conventional cumulative exposure (because risk varies with the square of the exposure). The authors found that even brief exposure to high concentrations (2 mg/m³) greatly increased the risk. By the same token, in a study of workers employed in the pottery, refractory, and sandstone industries of Stoke-on-Trent, Cherry et al. (1998) found that while cumulative exposure and average

concentration were strongly related to presence of small opacities, duration of exposure was not. Thus, the assumption that cumulative exposure is the relevant metric even when there are huge differences in exposure concentration and exposure duration between occupational studies and the environmental setting is questionable.

(2) The extrapolation from the occupational to the environmental setting also assumes there is no concentration threshold below which silicosis will not be induced. That is, OEHHA's derivation of the REL assumes the exposure-response curve maintains a slope at low cumulative exposures, whereas it is likely that a threshold model would give as good a fit as a curvilinear one at these low exposures.

Response. *Health risk assessment usually involves extrapolation often between species, from high to low doses (possibly over several orders of magnitude), and from healthy workers to the general population. In this risk assessment the extrapolations needed are from higher to lower doses (but only over approximately one order of magnitude) and from workers to the general population. As for the latter, there are so many workers (17,300) in the studies cited that the Uncertainty Factor used for intraspecies variability (UF_H =3) is smaller than usually used (default UF_H = 10). After extrapolating from workplace exposure to ambient exposure and allowing for sensitive human subpopulations, it is reasonable that "the proposed REL of 3 micrograms per cubic metre is at least one order of magnitude lower than the median/average exposure of workers in the various industries studied."*

A dose rate effect is possible, but would be less crucial at the lower concentrations important for the development of a chronic REL for silica. The exposure to silica in the Scottish collieries (Buchanan et al., 2001) was unusually high and of least relevance to a chronic REL.

The extrapolation from the occupational to the environmental setting does not imply a no threshold assumption. Setting a REL is based on a concept of a threshold below which adverse effects are not likely. And although workplace standards are called Threshold Limit Values (TLVs), some workers experience adverse health effects at or near the TLV.

Comments on Specific Sections of the Chronic Toxicity Summary.

Comment 4. Section IV. Effects of Human Exposures (Page 2).

1. The CTS refers to the occurrence of small airways obstruction in the absence of radiological changes based on observations by Chia et al (1992). It should be noted that Chia et al also state: "The clinical and prognostic significance of airways obstruction is still far from clear. Further studies would be required to evaluate its predictive value in identifying workers who will develop clinical airflow obstruction."

In this study, none of the 140 workers employed in a granite quarry had small opacities greater than ILO 1/0. Evidence that pulmonary function changes related to increasing exposure was based on a comparison of low exposure workers (clerical workers), transport/maintenance

workers (moderate exposure) and drillers/crushers (high exposure). It is questionable whether clerks constitute an appropriate comparison group for manual workers. It also should be noted that this study is limited in size (140 persons), is cross-sectional, and exposure levels were not quantitatively defined. While smoking differences were not significantly different between exposure groups, they were certainly not the same - with the % smokers increasing from 30.6% to 56.0% to 61.9%, and pack-years increasing from 377 to 453 to 553 from the low to high exposure groups respectively. Age also increased from 36.1 to 44.0 to 48.6 from the low to high exposure groups. Age correlated highly with duration of employment and with smoking. As the relationship between pulmonary function changes and radiological change was not reported, it is not known whether the observed pulmonary function changes relate to radiological changes or whether these pulmonary function changes might be observed at the same rate in a non-exposed general population of similar age and smoking habits.

The real issue is whether or not there are pulmonary function changes or clinical disease at levels of radiological change of ILO small round opacities of below 1/0 or 1/1. The use of "not yet well understood pulmonary function changes" as indices is not appropriate because we do not know that they are indicative of silica-related disease in the long term. It is noteworthy that the results of an autopsy study by Hnizdo et al (1994) did not find any significant association between autopsy findings and lung function impairment, although the fact that low exposure workers did not have the lung function test may have been a factor. The degree of emphysema was also unrelated to duration or cumulative exposure in gold mining.

2. The CTS notes that in some cases, silicotic nodules not detected radiographically are found at autopsy. The autopsy diagnosis is important if the autopsy findings relate to clinically important or life-shortening effects. Autopsy findings that have no clinical significance are, at least at this time, unimportant. The variability in pathological observations in the studies of silicosis is generally not known.

Response. *Chia et al. (1992) may not be the best study to make the point that small airways obstruction can occur in the absence of radiological changes. However, the American Thoracic Society (1997) states: "Studies from many different work environments suggest that exposure to working environments contaminated by silica at dust levels that appear not to cause roentgenographically visible simple silicosis can cause chronic airflow limitation and/or mucus hypersecretion and/or pathologic emphysema." (American Thoracic Society 1997. Adverse effects of crystalline silica exposure. Am Respir Crit Care Med. 155:761-5.). Epidemiologically the chronic airflow limitation due to silica exposure can be detected above levels expected to be due to smoking.*

In regard to autopsy findings, Hnizdo et al. (1993) found that among their South African gold miners with less than an ILO category of 1/1 (i.e., 1/0, 0/1, and 0/0) nearly half showed varying (slight, moderate, or marked) levels of histological silicosis at autopsy.

	Reader 1	Reader 2	Reader 3
ILO category < 1/1	*426*[a]	*428*[a]	*475*[a]
No silicosis at autopsy	*153*	*150*	*151*
Insignificant "	*75*	*73*	*75*
Slight "	*123*	*126*	*142*
Moderate "	*63*	*67*	*88*
Marked "	*12*	*12*	*19*
Marked + moderate	*75/426 = 17.6%*	*79/475 = 16.6%*	*107/475 = 22.5%*
Marked+mod+slight	*198/426 = 46%*	*205/475 = 43%*	*249/475 =52%*

[a] *Each reader read the same 557 radiographs. The remaining were classified as ≥ 1/1.*

OEHHA staff agrees that autopsy diagnosis is important if the autopsy findings relate to clinically important or life-shortening effects. However, we do not know, if, for example, those in the "marked silicosis" at autopsy category died younger or had worse pulmonary function than those in other categories.

Comment 5. A. Environmental Silicosis (Pages 2-3).

The environmental concentrations summarized here are as high or higher than those encountered occupationally and are restricted to certain locations of the world. Progressive Massive Fibrosis is not associated with low exposures. The data from Saiyed et al (1991) should not be presented as a generalized statement of the risks of environmental silica exposure but are nevertheless environmental and provide evidence that naturally occurring silica combined with wind can produce environmental conditions significantly worse than encountered in occupational settings. A concentration of 7.5 mg/m^3 of dust containing 70% quartz is 5,250 μg/m^3 of respirable quartz. This is more than an order of magnitude higher than typical occupational exposures and three orders of magnitude higher than environmental exposures that might be expected in the United States. Thus, the data from Saiyed et al (1991) are of no relevance in the present context.

Response. *The data from Saiyed et al. (1991) are presented as part of the extensive data available on silica health effects. The data were not used to derive the cREL or to imply that we anticipate environmental silicosis in California.*

Comment 6. B. Occupational Silicosis.

This section of the report describes studies of silica and silicosis, but with limited critical evaluation. Critical evaluations of most of these studies are given in the report by Gibbs et al (1999), attached as Appendix A. A few brief observations on these studies are offered below.

1. Hard Rock Miners in Ontario (Muir et al 1989).

On page 4, it is stated that the shallowness of the dose-response relationship in this study is "due in part to the lack of follow-up of members who left the mines". We suspect that this is a factor, but it is not in fact known to be the case.

2. <u>Gray iron foundry workers (Rosenman et al 1996)</u>.

   This is an important study in that it evaluates a sand using industry. However, some workers had exposure to asbestos and were exposed to mixed dusts. Midget Impinger dust concentrations were converted to respirable mass dust concentrations assuming the same factor as used in the granite industry. The validity of this is not known. Airborne silica concentrations were calculated using the bulk silica content of the sands, raising questions about the exposure levels used in the study.

3. <u>Diatomaceous earth workers in California (Hughes et al 1998; Park et al 2002)</u>

   The following statement on page 6 of the CTS is not comprehensible: "However, since radiography can under-diagnose silicosis, complete accounting for silicosis will require evaluation at autopsy." Epidemiologically, chest radiographic changes are used as an indicator of silicosis. Diagnosis requires clinical and or pathological evaluation. To prevent the disease, we do not need to know the absolute level of disease, only that our indicator, the radiograph, reflects the occurrence of the disease whether measured clinically or pathologically. This is the case with silicosis.

   It is interesting to note that if the results presented by Hughes <u>et al</u> are adjusted to have the same definition of silicosis as that in the Ontario hard rock miners study, the cumulative risk of silicosis at 0.1 mg/m^3 respirable silica in the two studies is quite similar (2.1% in Hughes <u>et al</u> and 1.2% in the Ontario hard rock miners).

   It is not clear why the criteria used to convert dust concentrations in the mortality and radiological studies of Diatomaceous Earth (DE) Workers, as described are different. In their paper reporting mortality, Checkoway <u>et al</u> (1997) stated that the estimates of crystalline silica content were 1% for uncalcined DE, 10% for calcined DE and 20% for flux-calcined DE. However, Hughes <u>et al</u> (1998), reporting radiological changes, noted that the values were 3%, 20% and 60% for natural, calcined and flux calcined respectively. In both studies, it appears that the conversion was based on bulk product cristobalite content, not on measurements of respirable cristobalite. Both these factors raise questions about the reliability of the exposure estimate - which is unfortunate, as this is a well conducted study.

4. <u>South African Gold Miners (Hnizdo and Sluis-Cremer,1993)</u>

   As noted at the beginning of these Comments, this is the key study being used to establish the REL. These data need to be recalculated based on the underestimation of quartz exposure. As the relationship is curvilinear, this will make a substantial difference in the estimated risks at low exposure levels, which are the ones more relevant for developing an environmental standard.

5. <u>Hong Kong Granite Workers (Ng & Chan 1994)</u>.

   It should be noted that the original authors commented on the potential biases in this study and lack of precision in work histories and exposure estimates.

6. Scottish Coal Workers (Miller et al 1998).
        I have no comment. When we evaluated the various studies in the report attached as Appendix A, we decided that coal industry studies were not appropriate for establishing silica standards.

7. Gold Miners in South Dakota (Steenland and Brown 1995).
        The authors of the CTS quite correctly point out the problem of mixing mortality with radiological outcome data. (A more complete critique of this study is given in Gibbs et al 1999, Appendix A hereto, pages 60-61). The method of analysis used by Steenland and Brown is not appropriate, as the dates of incidence were unknown for those defined as having silicosis through death certificates. For example, of the 52 miners with an exposure exceeding 4 mg/m^3-years, 26 had silicosis by the definition in the paper. The cumulative risk was thus 50% not 84% as calculated by the life-table method. The risks in this paper are overestimates of actual risk because of the use of prevalence rates as if they were incidence rates. This should be taken into account when evaluating the results from this study.

8. Miners in Leadville, Colorado (Kreiss and Zhen 1996).
        The authors of the CTS quite correctly point out the small size of the population. However, the broader issues are questions of the extent to which this small population is representative of the many thousands of workers who worked in the mines in Leadville, Colorado. In addition, there are major weaknesses and uncertainties in the exposure assessments for this study. A more detailed critique of this study is given by Gibbs et al (1999), Appendix A hereto, pages 41-45.

9. Chinese Tin Miners (Chen et al 2001).
        The percentage of crystalline silica in the respirable dust in this study was only 3.6%. This is a very low percentage compared to that in the other studies cited. Thus, the workers in this study were exposed to high concentrations of other respirable substances in the dusts. It is interesting to note that in coal mines, Walton et al (1977) reported no quartz-related effect from dusts containing less than 10% quartz. In the Chinese tin miners study, it was also necessary to convert the Chinese radiograph readings to readings using the ILO scale, further limiting the relevance of this study for determining exposure-response relationships for silicosis and establishing a REL.

10. Industrial Sand Workers (McDonald et al 2001, Hughes et al 2001, Rando et al 2001).
        This is a mortality study. The reliability of silicosis diagnoses on death certificates can be questioned without radiological or pathological evidence of silicosis. I do not understand the relevance or meaning of the statement that these mortality odds ratios are in general agreement with those in the radiological study of Rosenman et al (1996).

11. Silica Particle Size.
        This is a summary of measurements of particle sizes. Particle size is likely to be very important in terms of evaluation of community air risks, yet this section only reports on the occupational dust. It would be useful to know how the particles sizes in the community air differ from those in the workplace.

Response. *Staff read the paper "Assessing the risks of non-malignant respiratory disease in workers exposed to silica" by Gibbs, Berry, and Muir. Staff appreciates the clarifications in that paper and in the critical comments made by the commentator about the various studies. The following address some specific points made above.*

In regard to point 3, the statement "However, since radiography can under-diagnose silicosis, complete accounting for silicosis will require evaluation at autopsy" refers to the observation that many cases of silicosis determined by autopsy occurred in patients who had not shown abnormal radiographs. Hnizdo et al. (1993) reported that a large proportion of those with a moderate and marked degree of silicosis as determined by autopsy were not diagnosed as silicotic by chest radiographs.

In regard to point 4, OEHHA staff believes that due to the variability that has been reported for % quartz in the South African mine dust there is no justification in using only the value of 54% recalculated by DuToit and Gibbs (2003). (See our response to Comment 1 above.)

In regard to point 10, the statement meant that for similar cumulative exposures there were similar odds ratios in the studies. For example, in Rosenman et al. a cumulative exposure of 6 (mg/m^3)-y had an odds ratio similar to that from Hughes et al. for a median exposure of 6.916 (mg/m^3)-y.

Comment 7. <u>Risk estimation for silicosis from epidemiologic studies (Page 15</u>**).** This section consists of a table summarizing risk estimates from various authors. I assume that values have been correctly copied from the various papers so I have not checked the values in this table to verify them.

Response. *Staff checked the values several times for correctness. In the Public Comment version of Table 13, the value of 3.4 in column 3 of Hughes et al., 1998, should be 3.7. The change has been incorporated into the revised summary in what is now Table 14.*

Comment 8. <u>Determination of Lowest Observed Adverse Effect Level (LOAEL) and No Observed Adverse Effect Level (NOAEL) for silicosis (Rice and Stayner, 1995).</u> This subject is discussed in some detail on pages 73 -75 of Gibbs <u>et al</u> (1999), Appendix A hereto. The following should be considered before accepting these values.

a. The estimates of the NOAEL in the paper by Rice and Stayner as reproduced in this table are not correct. They stated that Hnizdo and Sluis-Cremer (1993) reported no cases of silicosis among 2,218 gold miners with dust exposures less than 1 mg/m^3-years of cumulative dust exposure, and they calculated a NOAEL of 7 $\mu g/m^3$ respirable silica for 45 years, as the silica content of the gold mine dust was given as 30%. (<u>i.e.</u>, 1000/45 x 0.3 = 6.666). In fact, in Table 4 of the paper by Hnizdo and Sluis-Cremer (1993), there were no cases in the range for which the

<u>mid-point</u> was 1 mg/m³-yr. As the mid-point of the next range was 3 mg/m³-yr cumulative dust exposure, then the first range was presumably from 0-2 mg/m³-yr cumulative dust exposure. A total of 2,014 miners went through this range without a finding of silicosis, so there were no cases below 2 mg/m³-years of cumulative dust exposure, which gives a NOAEL of 13 μg/m³ of respirable silica dust (<u>i.e.</u>, 2000/45 x 0.3 = 13.33). Furthermore, since the respirable dust exposure in the South African studies is based on acid washed dust only, this figure is likely to be higher when adjusted to take account of all the other dust incorporated in the gravimetric respirable mass determinations. These South African study estimates need to be re-calculated after a re-analysis of the data, making appropriate adjustments for the approximately 2-fold underestimate of quartz exposure (<u>see</u> Gibbs and Du Toit 2002, attached as Appendix A).

b.   The table includes estimates based on the studies by McDonald and Oakes. It should be recognized that the gold mine mentioned here is the Homestake Mine studied originally for cummingtonite-grunerite mortality effects. In the original study, of which I was a co-author, workers were classified into very low, low, moderate, high and very high exposure categories based on approximate estimates of exposure for various job categories. McDonald and Oakes in their paper recognize this by labeling the column describing the exposures in mppcf as an "assumed level". The original study was based on midget impinger measurements, and no mass equivalent was reported. McDonald and Oakes note the fact that the results were based on midget impinger counts and also provide a gravimetric equivalent, which they quite properly describe as "approx". However, they do not describe how they converted the midget impinger values to gravimetric measurements. They may have used a conversion factor based on the Vermont granite industry, but that would understate the gravimetric values because, as they note, the airborne dust at the Homestake mine was reported to have a free silica content of 39% while the Vermont granite dust had a silica content of only 10%. McDonald and Oakes conclude with the observation that "the main uncertainty in [their] analyses of exposure-response stems from unreliable estimates of the former, rather than the latter." Nevertheless, they believe their results suggested "that the relativities in the exposure estimates were probably valid, despite questions as to levels in absolute terms." As the co-author who developed the exposure assignments in the Homestake Mine study, I can attest that this is a fair assessment. The derivation of a precise LOAEL from the study by McDonald and Oakes is not warranted.

It also should be noted that the silicosis models are curvilinear, with risk increasing as exposure increases from zero. Within the low exposure range, the increase in risk as one moves up the exposure curve is low; thus, a threshold model would have given a good fit to the data.

Response. *The NOAEL and LOAEL values in Table 14 are taken directly from Table 2 of Rice and Stayner (1995). OEHHA staff appreciates the commentator's critique of the data. An indication has been added to the table that McDonald and Oakes considered their values as approximations only. The values in Table 14 were not used in the derivation of the chronic REL for crystalline silica.*

In regard to the selection of the correct NOAEL for the Hnizdo and Sluis-Cremer (1993) report, OEHHA staff has revised the NOAEL from 1 to 2 mg/m³-years of cumulative dust exposure. The data indicate that there were no cases of silicosis up to 2 mg/m³-yr. Thus 2 mg/m³-yr can be

considered the NOAEL from the study, and our document reflects this change from the public review draft. It should be noted that the NOAEL does not enter into the derivation of the REL because the REL is based on the benchmark dose calculation. Thus the change in our document of designating 2 rather than 1 mg/m³-yr as a NOAEL study does not change the chronic REL. However, staff does not agree with the commentator's calculation above that the human NOAEL would be 13 µg/m³ [2,000 (µg/m³-yr respirable dust)/45 years x 0.3 = 13.33], because the commentator used 45 years (maximum work-life) rather than the study's average of 24 years dust exposure. Use of 24 years would result in a value of 25 µg/m³. If one were to utilize the NOAEL/UF approach to estimate the REL, use of time extrapolation (25 µg/m³ x 10 m³/20 m³ x 5 d/ 7d x 48 wk/52 wk) with this NOAEL leads to a value of 8 µg/m³ under the assumption of 30% silica in the mine dust. Application of a UF_H of 3 to protect other sensitive humans would result in a chronic REL estimate of 3 µg/m³. ,the same value derived by OEHHA using the benchmark dose approach.

In regard to the correct percentage of quartz in the mine dust, OEHHA staff has reviewed the paper by Gibbs and Du Toit (2002) for possible application to the chronic REL derivation. These authorsstate that the percent quartz in the South African gold mine dust in the Hnizdo and Sluis-Cremer (1993) study should be increased by a factor of 1.8 (54% rather than 30%). ("In the absence of systematic side-by-side thermal precipitator and modern respirable mass measurements in the South African gold mines, the true relationship between the respirable mass concentrations and the theoretically derived concentrations cannot be known. However, with many uncertainties, we estimate that the quartz exposures of South African miners derived from past theoretically based conversions from particle number to respirable mass underestimate the actual quartz exposures by a factor of about 2." Two was rounded up from 1.8 in the text.)

For the estimate of 30% silica in the South African gold mine dust, Hnizdo and Sluis-Cremer (1993) relied on estimates for the years 1956-1960 by Beadle (Beadle and Bradley, 1970; Beadle, 1971). The original data, obtained by Corner House Laboratories for the South African Bureau of Mines, are partly presented by Beadle and Bradley (1970), but a more detailed presentation of exposures for various classes of workers is given by Page-Shipp and Harris (1972). The latter paper also describes in some detail the methodology used to obtain the particle counts, and to convert those data into either respirable surface area or respirable mass values. Gibbs and Du Toit (2002) reviewed the data and methodology used by Hnizdo and Sluis-Cremer (1993) to estimate silica exposures of workers, which apparently depended on an unpublished analysis by Du Toit of the Corner House Laboratories' data. Gibbs and Du Toit accept the estimates by Beadle and Bradley (1970) of the quartz percentages in the dust, i.e. 54% for incinerated and acid-washed dust and 30% for unmodified dust. However, they assert that Hnizdo and Sluis-Cremer (1993) incorrectly applied the 30% (total dust) silica content to figures for acid-treated dust in calculating the silica exposures of each occupational group. This contention is presumably based on the footnote to Table II in Hnizdo and Sluis-Cremer (1993) where the respirable dust concentration is described in a footnote as "After heat and acid treatment".

In order to clarify this point, OEHHA reviewed the independent reporting of the underlying data by Page-Shipp and Harris (1972). For most occupational groups, the silica exposures (shown in Table 19 of the revised chronic REL summary) calculated from Appendix I of Page-Shipp and Harris (1972), using the 54% silica content appropriate for acid-washed dust, correspond more closely to those calculated by Hnizdo and Sluis-Cremer (1993) (applying the 30% quartz content to their reported "respirable dust concentrations"), than to the modified, and higher, quartz exposures proposed by Gibbs and Du Toit (2002). For example, 113 exposure samples were taken for stopers. The time per shift was 7.8 hours (Page-Shipp and Harris, 1972, Table III, last row), the cumulative exposure was 1.57 mg/m^3-hours, and the average exposure level was 0.20 mg/m^3. If 54% of this were quartz, the quartz level would be 0.11 mg/m^3. Table II of Hnizdo and Sluis-Cremer (1993) lists 0.37 mg/m^3 respirable dust for stopers. Thirty % of 0.37 mg/m^3 equals 0.11 mg/m^3, the same value reported by Page-Shipp and Harris. In Table 4 of Gibbs and Du Toit (2002) stopers are also reported to be exposed to 0.37 mg/m^3 respirable dust. If 54% were quartz, as Gibbs and Du Toit contend, the quartz level would be 0.2 mg/m^3. For 6 of the 9 categories of workers comprising 83% of the samples taken the silica levels correspond more closely to values used by Hnizdo and Sluis-Cremer than to those suggested by Gibbs and Du Toit. Thus OEHHA staff concluded that the 30% used by Hnizdo and Sluis-Cremer was likely correct. Dr. Hnizdo reviewed our analysis and agrees with our interpretation of the data (Hnizdo, personal communication, October 2004).

Finally, the comment seems to imply that OEHHA used a nonthreshold model to derive the chronic REL. The benchmark dose methodology does not necessarily imply a non-threshold model, regardless of the curve form used to fit the dose-response curve. (In any event, in this particular case the log dose/probit model which is usually regarded as a threshold model, was used to fit the response data.). Deriving a REL implies a threshold below which an adverse effect is not anticipated.

Comment 9. Proposals to change the occupational exposure limit. It is not clear why this section appears in the CTS, which is concerned with developing a non-occupational exposure standard.

The CTS cites three papers as supporting a change in the occupational exposure limit. It should be noted that Mannetje et al (2002) pooled the results of several studies which included the US Diatomaceous earth workers, U.S. and Finnish Granite workers, US sand workers, US gold miners and Australian Gold miners. While this analysis showed that high exposure can result in death from silicosis, mortality data for an endpoint such as silicosis are not likely to be reliable. Unless there are radiological or autopsy data available, the death certificate diagnosis of silicosis is likely to overestimate the risk. The reason for this is that compensation is probably easier for a family to obtain if silicosis is mentioned on the death certificate.

There are also some unresolved issues relating to exposure in the studies used by Mannetje et al (2002). Were the Finnish Quarry workers really exposed at concentrations 10 times greater than workers in the US granite sheds? What were the factors used in the cristobalite studies to convert the respirable dust concentrations to respirable cristobalite? Seixas

et al are cited, but they did not do the conversion to cristobalite; they only estimated respirable dust exposure. Furthermore, as mentioned earlier (*see supra*, p. 5), it is not clear why the criteria used to convert dust concentrations in the mortality (Checkoway et al, 1997) and radiological studies (Hughes et al, 1998) of Diatomaceous Earth (DE) Workers appear to be different. Moreover, in both studies, it appears that the conversion was based on bulk product cristobalite content, not on measurements of respirable cristobalite.

As far as the recommendation by Greaves (2000) is concerned, this appears to be based on the study by Kreiss and Zhen (1996), which the CTS appropriately does not consider adequate. Gibbs et al (1999), Appendix A hereto, pages 41-45, provides many additional reasons why it is not appropriate to use that study as the basis for establishing a standard.

Response. *The section on "Proposals to change the occupational exposure limit" is presented for information and comparison purposes. An occupational exposure level is intended to protect generally healthy workers from the adverse effects of exposure 8 hours per day, 5 days per week over a working lifetime. A chronic REL is intended to protect the general public, including sensitive individuals, 24 hours/day, 7 days/week. A chronic inhalation REL, which equaled or exceeded the occupational exposure limit, would not be taken seriously. How much below the occupational exposure limit the chronic REL is set will depend on the data available to calculate the REL. It is relevant to note that there are concerns in the published scientific literature that the current occupational standard is not adequately protective of workers.*

Comment 10. Silica exposure and lung cancer. As the REL is based on studies of non-malignant respiratory disease, a discussion of lung cancer risk is not needed. However, it should be noted that the prevention of silicosis is a practical step in the elimination of any lung cancer risk that may exist.

Response. *The mention of silica exposure and lung cancer is presented for completeness. IARC has designated crystalline silica (inhaled in the form of quartz or cristobalite from occupational sources) as an agent known to cause cancer in humans. The prevention of silicosis is a practical step in the elimination of at least some of the lung cancer risk. However, according to Checkoway and Franzblau, "The association between silica and lung cancer is generally, but not uniformly, stronger among silicotics than nonsilicotics. However, the existing literature is ambiguous due to incomplete or biased ascertainment of silicosis, inadequate exposure assessment, and the inherently strong correlation between silica exposure and silicosis which hinders efforts to disentangle unique contributions to lung cancer risk." (Checkoway H, Franzblau A. Is silicosis required for silica-associated lung cancer? Am J Ind Med. 2000 Mar; 37(3):252-9.)*

Comment 11. VI Derivation of Chronic Reference Exposure Level (REL) The key study is that of Hnizdo and Sluis-Cremer (1993). However, as noted earlier, it has several limitations which should be recognized, and the study should not be used as the basis for standard setting until they have been resolved.

The most fundamental problem is the exposure estimate. Gibbs and Du Toit (2002) have recently revisited the exposure estimates used for the South African studies. (See Appendix B hereto.) This is particularly significant, because Dr. Du Toit was one of the main authorities who advised Dr. Hnizdo concerning dust and silica exposure. The main finding in this paper is that exposures of the South African gold miner cohort were underestimated by a factor of about 2. When an appropriate adjustment is made to the Hnizdo and Sluis-Cremer data, it is found that a cumulative risk of 1.4% would have corresponded to an exposure of about 2.7 mg/m^3-yr respirable silica. As it turns out, this is not that different from the estimate based on the Ontario miners study of 1.2% at 4.0 mg/m^3-yr respirable silica. The difference in risk would be quite in line with an underestimate of risk in the Ontario mining study because of lack of follow-up after men left the industry.

As pointed out earlier, the NOAEL based on the South African data is not correct - it should be 13 μg/m^3 of respirable silica. This figure will change again (presumably doubling to 26 μg/m^3) when an adjustment is made for exposure underestimation. The other values presented in Section VI of the CTS to derive a REL on the basis of the Hnizdo and Sluis-Cremer study will need to be re-calculated taking into account the correction of the exposure level.

The second limitation of the Hnizdo and Sluis-Cremer study is the fact that results are based on one x-ray reader who was chosen because his readings best correlated with the observations of a pathologist examining autopsy material. The problem with this is that there is no measure of the observer variation associated with the pathological or radiological readings.

Response. *OEHHA staff noted the second limitation (use of one x-ray reader) in the chronic REL summary. In regard to the exposure estimates, as noted above in OEHHA's response to Comment 1 there are other estimates of percent quartz in the dust from the South African gold mines, which indicate that values lower than the 30% stated in Hnizdo and Sluis-Cremer (1993) are also plausible. Thus, OEHHA's proposed REL is based on estimates of the silica content of dust provided in the original paper; this estimate falls about mid-range of other estimates of the silica content.*

Comment 12. OEHHA cites the study of South Dakota gold miners by Steenland and Brown (1995) as supportive of the REL. Unfortunately, that study, as pointed out in the CTS, was a mixed radiological/mortality study. The date of onset of the radiological changes (if there were any) are not known for those identified as silicotics on the basis of death certificates. In addition, there are major uncertainties in the exposure assessments for this study. Moreover, it should be noted that this mine also was studied for the effects of cummingtonite-grunerite, which could influence the occurrence of irregular opacities. Further, the life-table analysis method is not valid for mixed incidence/prevalence data. In any event, as OEHHA notes in the CTS, none of

the BMDS models gave an acceptable fit to the data from this study. All things considered, Steenland and Brown (1995) cannot be used to derive (or to support) a REL.

Response. *The paper by Steenland and Brown (1995) has weaknesses as staff noted in the CTS, yet a dose-response was seen. In regard to fitting BMDS models to their data, as stated in the revised chronic REL summary: "In risk assessment, the highest dose or doses are often dropped in order to obtain an acceptable fit of the model to the data. This is reasonable with the benchmark approach since the highest doses should be least informative and the doses in the low dose region near the benchmark should be most informative (USEPA, 1995; Filipsson et al., 2003)". Fitting the probit model to the log dose of the five lowest silica levels from Steenland and Brown yielded a BMC_{01} of 0.34 (mg/m^3)–yr CDE $(\chi^2 = 1.32; p$ value for fit = 0.5177). [For comparison, $BMC_{05} = 0.85$ (mg/m^3)–yr CDE.] Fitting the quantal quadratic model gave a BMC_{01} of 1.02 (mg/m^3)–yr $(\chi^2 = 3.36; p = 0.3395)$." It should be noted that, since they did not have much, if any, autopsy data, Steenland and Brown likely underestimated (rather than overestimated) the prevalence of silicosis by use of death certificates.*

Comment 13. The other study mentioned as being supportive is that of Hughes et al (1998), which involved workers exposed to cristobalite in a diatomaceous earth facility. The authors analyzed the data in part by separating workers who were exposed to average silica concentrations $\geq$ 0.5 mg/m^3 (primarily pre-1950 hires) from workers who were exposed to average silica concentrations $\leq$ 0.5 mg/m^3 (primarily post-1950 hires). Hughes et al found that at 2.0 mg/m^3-yrs, the rate of small opacities 1/0 or more for workers exposed in the later years was 1%, which they noted "is not appreciably higher than that reported for many unexposed populations" among whom a substantial prevalence of idiopathic small opacities has been found. In particular, two reviews of the literature on irregular opacities indicate substantial idiopathic small opacities in non-exposed populations, and a pooled prevalence of 1.3% was reported in North American men. (Meyer et al. (1997); Dick et al (1992)). OEHHA, however, says that it considers the 6 cases in the "less than 1 mg/m^3-yr category of exposure" to be silica related. This is unlikely to be correct. Hughes et al included irregular as well as rounded opacities in their radiograph readings. Since the background rate findings for idiopathic small opacities discussed above are for irregular opacities, it seems likely that the 1/0 readings by Hughes et al at the less than 1 mg/m^3-yr level (which was similar to the pooled prevalence rate in non-exposed North American men) were irregular opacities, which would *not* be silica-related. Indeed, the same is likely to be true of the opacities observed in workers at the 2.0 mg/m^3-yrs level whose average exposures were $\leq$ 0.5 mg/m^3. As OEHHA observes on page 2 of the CTS, silicotic nodules are "histologically unique." For these reasons, the "less than 1 mg/m^3-yr" exposure category in Hughes et al should not be considered a LOAEL. (This view is supported by Dr Geoffrey Berry in comments he has prepared on the CTS.) In fact, it could be argued that the 2.0 mg/m^3-yrs level was a NOAEL for workers whose average exposures were $\leq$ 0.5 mg/m^3. Finally, as noted above, there are problems with exposure estimation in this study.

Response. *It seems likely to the commentator that the 1/0 readings by Hughes et al. (1998) at the less than 1 mg/m^3-yr level were irregular opacities. However, the authors of the study did not discuss specifically in their paper the shape of the opacities seen on the radiographs of the*

six workers at the less than 1 mg/m^3-yr level. In the absence of a definitive statement it is prudent from the viewpoint of public health to assume that the opacities were due to silica exposure. In addition, the very beginnings of some silicotic nodules may be irregular opacities. In fact Dick et al. (1992) state: "The development of irregular opacities is also related to exposure to various mineral and other dusts, and although their prevalence increases with cumulative dust exposure, in general the type of dust, whether fibrogenic or relatively inert, seems to be of little moment." Presumably quartz might be one type of dust involved.

Comment 14. In the discussion of the South African study on page 21 of the CTS, OEHHA states that "the endpoint measured in this epidemiological study is considered severe, since it represents the occurrence of clinically recognizable and irreversible disease". OEHHA should provide the basis for the statement that the endpoint measured in Hnizdo and Sluis-Cremer represents clinically recognizable disease. It was our reading of the literature that there was no evidence of silica-related pulmonary function effects or clinically significant disease at profusion categories of 1/1 small rounded opacities or below (See Gibbs et al 1999, Appendix A hereto, pages 56-57 and 77). Moreover, in a separate paper, Hnizdo (1992) found that smoking is far more strongly associated with loss of lung function than dust exposure in the South African gold miners and that longitudinal loss of FEV$_1$ and FVC was not related to cumulative exposure to dust.

Response. *OEHHA considers that silicosis is a severe endpoint because of the irreversible and progressive nature of this pneumoconiosis, even after exposure has ended. The American Thoracic Society (ATS, 1997) states: "Studies from many different work environments suggest that exposure to working environments contaminated by silica at dust levels that appear not to cause roentgenographically visible simple silicosis can cause chronic airflow limitation and/or mucus hypersecretion and/or pathologic emphysema." In epidemiological studies, airflow limitation due to silica exposure can be detected above levels expected to be due to smoking.*

Comment 15. On page 22 of the CTS, the authors address the question of whether radiological studies show background rates of radiological changes in the general population. The answer is "yes." This is one justification for using 1/1 as the cut-point and for defining radiological silicosis as 1/1 small round opacities. This would exclude the effects well described as smoking and other dust related effects in the general population. At a cut-point of 1/1, the background rate of small opacities would not be an important factor. This becomes particularly important at low exposures, which is the level under consideration in the CTS. In fact, Hnizdo suggested that one could improve the overall accuracy of radiological readings by using 0/1 as the cut point for high exposure workers and 1/1 for low exposure workers. This is very relevant to establishing criteria at the levels of exposure now under consideration for occupational and environmental settings.

Response. *The commentator may be referring back to his concern expressed in Comment 13. A few irregular opacities on a radiograph may be considered background noise due to age, smoking, or other causes. However, as noted in our response to Comment 13, OEHHA staff does*

not consider it proper public health policy to consider small round opacities in workers exposed to silica as background, rather than as the result of low level, workplace silica exposure, nor to assume that small opacities were likely to have been irregular rather than round. .

Comment 16. On page 23, paragraph (3), the CTS refers again to the LOAEL of 8 μg/m^3 based on McDonald and Oakes (1984). As noted earlier, these authors warned about the approximate nature of their exposure estimates. It is not appropriate to use the values based on their studies to reach such precise quantitative conclusions.

Response. *Staff added a footnote to Table 14 to indicate the approximate nature of the exposure estimates in McDonald and Oakes (1984).*

REFERENCES NOT CITED IN THE CHRONIC TOXICITY SUMMARY

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Walton W.H., Dodgson J., Hadden G.G., Jacobsen M. (1977). The effect of quartz and other non-coal dusts in coalworkers' pneumoconiosis. Part 1: Epidemiological Studies. Inhaled Particles 1V, W.H. Walton Ed., pp 669-690.